1900

TWO CASES OF POST-TYPHOID ANÆMIA,

WITH REMARKS ON THE VALUE OF EXAMINATIONS OF THE BLOOD IN TYPHOID FEVER.

By W. S. THAYER, M.D.,

First Assistant in the Medical Clinic of the Johns Hopkins Hospital, Baltimore, Md.

From the Johns Hopkins Hospital Reports, Vol. IV, No. 1, Baltimore, Md.

TWO CASES OF POST-TYPHOID ANÆMIA, WITH REMARKS ON THE VALUE OF EXAMINATIONS OF THE BLOOD IN TYPHOID FEVER.

By W. S. THAYER, M.D.,
First Assistant in the Medical Clinic.

While the changes in the blood during the course of typhoid fever have been studied by many observers, but little attention has been paid to the fact that a post-typhoid anæmia may in some instances become so profound as to be of itself a grave complication of the disease. Le Canu[2] (1837) found a diminution in the number of corpuscles in two cases of typhoid fever. Andral and Gavarret[1] (1840) called attention to the unusually large proportion of red corpuscles present at the beginning and throughout the first part of the febrile period, a condition which they thought was due to the fact that most of the patients were young and healthy individuals. They state that while a fall in the number of corpuscles takes place during the fever, it is unimportant and due largely to the treatment by bleeding. Simon[5] (1842) noted that while the blood at the beginning of the attack and during the febrile period showed a normal or increased number of corpuscles, there was an anæmia during convalescence. Bequerel and Rodier[7] (1844) denied that the proportion of red blood corpuscles was ever actually increased, and asserted that the effect of typhoid fever on the blood was the same as that of any severe disease, namely, a marked diminution in the number of red corpuscles, a diminution which was probably increased by the frequent venesections. Popp[8] (1845), in ten cases, noted that with a normal or increased number of corpuscles in the beginning there was a gradual diminution during the fever. Jansen[10], in 1847, described a case of fatal anæmia with enlarged spleen coming on after a fever which may have been typhoid. No examinations of the blood were noted. Otto[11] (1848) found also a moderate falling off in the number of corpuscles. Welker[14] (1854) found a slight anæmia in three convalescents; the lowest point reached was 3,200,000. Denis[15] (1859) found in one case, on the fifteenth day, a decided diminution in the proportion of red corpuscles as well as of the other albuminoid constituents of the

blood. Jaccoud[16] (1863) held that the red corpuscles suffered in typhoid fever just as they did in any acute disease. Ernesti[17] (1864) reported an interesting case of post-typhoid anæmia which deserves repetition. A man, aged forty-six, previously healthy, passed in the early fall through a severe fever which was associated with considerable diarrhœa. Though he recovered from the attack and was able to leave his bed, he was never strong enough to return to his occupation, and in February, on account of progressive loss of strength and œdema of the dependent parts, he entered the hospital (Greifswald). The most striking symptoms were the excessive pallor, the soft and rapid pulse and the œdema. The temperature was normal; the spleen was not enlarged. The anæmia increased steadily and the patient died five months later. There was diarrhœa at times, and during the last three weeks of the patient's life there was a moderate daily evening rise in the temperature. Four weeks before death, dulness on percussion with a prolonged expiratory murmur were noted just below the left clavicle. No mention is made of any examination of the blood. On autopsy, beyond undoubted evidence of a previous typhoid fever, freshly cicatrized ulcers, and the extreme emaciation and anæmia, there was found to be a marked atrophy of the mucous membranes of the ileum and jejunum. There were also areas of tuberculous consolidation in both lungs, a cavity as large as a walnut at the left apex, and fresh tuberculous pleurisy. Considering the history of the case, the author believes that the tuberculosis had no influence on the development of the anæmia, but was, on the other hand, itself secondary process. See[18] (1866) admits that the anæmia which develops in typhoid fever may be so severe as to materially retard convalescence. Gautier[23] (1874) notes an anæmia developing during the course of typhoid fever. Bonne[25] (1875) found a marked anæmia in two cases—2,500,000 and 2,400,000 red corpuscles per cubic millimetre. The lowest point in the latter case was reached on about the twentieth day, after which there was a gradual rise to normal. Sörensen[27] (1876), in eleven cases examined during the febrile period, found eight with more or less anæmia; while in three patients who were cyanotic and moribund, the proportion of red blood corpuscles was normal in two instances and somewhat increased in the third. These last three cases of Sörensen were doubtless instances of an actual condensation of the blood. That this condition does occur has been very clearly shown by

Brouardel[26] in his studies on the blood after purging and in conditions of inanition. The writer[53] has also reported two cases of a similar nature. Arnheim[30] (1879) in one case found but a slight change in the blood during the febrile period. Baxter and Willcocks[31] (1880), after examining the blood in six cases, state that "enteric fever, even where it directly threatens death, does not seem to affect either the number or the quality of the red corpuscles to any marked extent." All of the examinations, however, were made at the height of the fever. Zaeslein[32] (1881), in thirty-seven cases, noted that the number of red corpuscles in the cubic millimetre began to diminish perceptibly only after the fever had lasted for some time. As soon as the fever was over, if there was still a further diminution in the body weight, there was a slight temporary increase in the number of red corpuscles per cubic millimetre. As soon, however, as the body weight began to increase, that is, at the beginning of convalescence, there was a rapidly developing oligocythæmia, which was most marked at the time of the first appreciable increase in weight. This oligocythæmia is more severe than that occurring during the febrile period, and lasts usually for weeks and possibly for months; relapses and complications cause, of course, variations in these conditions. The post-typhoid polycythæmia, when it occurs, is due, he thinks, to a concentration of the blood from the loss of fluid constituents, while the post-febrile oligocythæmia is due to a more rapid increase in the fluid constituents of the blood than in the formed elements. Halla[33] (1883) in fifteen cases found during the febrile period a diminution in the red blood corpuscles amounting on an average to 200,000, while in convalescence he found a marked fall, the blood-count in one case being as low as 2,162,000. Laache[34] (1883) in thirteen cases found a constant diminution in the red corpuscles averaging 18 per cent. This was independent of hemorrhages or unusual complications. Malassez[36] (1883), as the result of numerous observations, says: (1) In typhoid fever the proportion of red corpuscles is subject to the same variations as in health; for instance, a severe diarrhœa may cause a marked temporary increase in their number; (2) apart from these fluctuations, the proportion of red corpuscles changes but little during the height of the fever, but falls markedly with defervescence, to rise again progressively after the beginning of convalescence. Robin,[35] on the other hand, is quoted by Hutinel[56] as saying that on examina-

tion of the urine during typhoid fever, one finds that those pigments which appear to be derived from the destruction of the hæmoglobin are found in normal or diminished quantities, while those which come from an increased corpuscular destruction are absent or very rare. If, however, there is an inflammatory process in connection with the typhoid fever, then the red corpuscles diminish in number and the pigments derived from them begin to appear in the urine. Holst[37] (1885) reports a case of typhoid fever complicated with a grave ("pernicious") anæmia in a young girl of 20 which ended fatally at about the beginning of the third week. The anæmia, however, apparently preceded the fever. Leclerc[38] (1887), in an interesting study of the effects of the cold bath, antipyrin and acetanilide on the blood in ten cases of typhoid fever, concludes that the cold bath alone has little if any effect on the blood corpuscles. While antipyrin has but a slight effect, acetanilide has a deleterious action. In the three cases treated with the cold bath alone, the diminution in the number of red corpuscles was moderate. Tumas[40] (1887) in twenty cases found that while the number of red corpuscles was normal or even increased at the beginning of the process, it diminished gradually during the fever, but showed a more marked and sudden falling off at the beginning of the afebrile period. This anæmia lasted for a considerable time, as the blood was restored very slowly to its normal condition. Hayem[41] lays more stress upon the importance of this post-typhoid anæmia. According to him, the number of corpuscles per cubic millimetre is but slightly modified during the first weeks of the disease. It oscillates between 4,500,000 and 5,000,000, and sometimes more, a fact which he thinks can only be explained by supposing a very slight destruction of corpuscles, or an actual condensation of the blood as a whole. This condensation, he thinks, cannot be doubted in some cases. He has, in fact, seen as a result of profuse sweating or very profuse diarrhœa, a sudden increase in the number of corpuscles to a point even above normal, in one case as high as 5,700,000, a phenomenon comparable to that which is seen in the algid stage of cholera. During the course or towards the end of the third week there is a rather sudden diminution in the number of red corpuscles, which have so far resisted the process of the disease. The continued fever is, he believes, the principal cause of this destruction of the red corpuscles, as in the milder cases there is but little change in the number of the colored elements. In one

case in which death occurred on the fifty-third day of the disease, the blood contained at that time only 2,500,000 red corpuscles with a corpuscular value of 1,950,000.

Hæmoglobin. With regard to the hæmoglobin, Welker,[13] Naunyn,[20] Quincke,[21] and Quinquaud[22] found little change in the amount of hæmoglobin during the febrile period. Arnheim[30] noted no great change in four examinations during the earlier part of the fever, but a slight diminution in one case in the fourth week. Leichtenstern[28] noted that during the fever in the first, second and third, or even fourth week, there was but little change in the amount of hæmoglobin, while with the beginning of convalescence the curve sank rapidly. He found in one case with a relapse a fall, followed by a rise during the relapse, with a second fall afterwards. He suggests that this post-febrile oligochromæmia is due to a more rapid increase in the water, albumin and salts in the blood than in the red corpuscles—*i. e.*, to a relative thinning of the blood, an opinion which agrees with that of Zaeslein. Laache and Tumas both note a considerable diminution in the amount of hæmoglobin, the curve running nearly parallel to that of the corpuscles, but being somewhat lower. Laache[34] (twelve cases) disputes the statement of Leichtenstern that the fall in hæmoglobin occurs in the beginning of the afebrile period. He found that in all but one case the minimum of hæmoglobin occurred towards the end of the fever. He asserts also that the fall is more gradual. Ollivier[39] mentions a case of chlorosis in a young girl apparently following typhoid fever. Hayem notes also that the oligochromæmia is relatively greater than the oligocythæmia.

Colorless corpuscles. Virchow,[9] in his article on the white corpuscles and leukæmia and also in the Cellular Pathology,[19] assumes that a certain amount of leucocytosis must follow the hyperplasia of the lymphatic tissues affected in typhoid fever. He quotes Allen Thompson,[6] who says that in about a dozen cases of an epidemic fever occurring in Edinburgh he found a distinct leucocytosis. It is probable, however, that this fever was typhus and not typhoid fever. He also quotes a case of Andral[1] in which the blood of a patient with typhoid fever, dying in the third week, looked like that which escapes from an abscess opened before maturity. This case was, however, complicated with pneumonia of the left lower lobe. Bonne[25] examined the blood of three cases and found in all a

small number of leucocytes during the height of the fever, but in two an increase at the beginning. In one of these the proportion of colorless to red corpuscles was 1 to 120 on the eighth day, but normul throughout the rest of the time. In the other case, which he saw first on the sixth day, he asserts that he found 47,000 leucocytes to the cubic millimetre, while on the seventh there were 62,000. On the following day there were but few leucocytes, and on the ninth in three counts (Hayem's method) he found none—an interesting and unique observation. It is worth mentioning, perhaps, that some of his other counts of leucocytes are unusually high. Bonne also found a slight temporary leucocytosis in one case at the beginning of convalescence; this was probably associated with certain suppurative complicating processes.

On the other hand it has been generally recognized by almost all recent observers, as well as by some of the older ones who have investigated this special point, that there is not only no increase in the proportion of colorless corpuscles (leucocytosis) during the fever, but that, on the contrary, there is rather a tendency toward a diminution in number at the height of the disease. Many of the older authors call attention to the fact that the fibrin in the blood is diminished during typhoid fever, in contradistinction to the increase always observed in acute inflammatory affections. Raciborski[3] in 1839, as the result of the inspection of the clot obtained from the first blood-letting in a large number of cases of typhoid fever, noted the almost complete absence of the buffy coat, a striking contrast to the increase which is always observed in acute inflammatory processes. He asserts that in a case of typhoid fever in which the buffy coat is well marked we may be sure that a complicating inflammatory process exists. Durozier,[12] Sörensen,[27] Halla[33] and Tumas[40] all note the absence of leucocytosis. Tumas thinks that the proportion of colorless corpuscles may be slightly diminished at the height of the disease. Hayem[41] finds that the leucocytes diminish appreciably during the fever, sometimes reaching a point as low as 1000 per cubic millimetre, often falling under 2000. Pee[42] found in two cases a diminution in the number of leucocytes. Ouskow[43] and Khetagurow[46] note also the diminished proportion of colorless corpuscles, the latter in three cases finding that the number of leucocytes fell gradually, reaching its lowest point (2500 to 3000) at about the end of the third week, and beginning at the end of lysis to return to the normal, which is reached by the sixth or seventh week.

In a considerable number of observations in Prof. Osler's clinic we have been able to confirm essentially the views of the majority of these writers. At the beginning of typhoid fever the blood shows generally a normal number of red corpuscles, and often, as the individuals are commonly strong and healthy, the upper limit of normal may be reached. During the height of the fever there is generally a moderate and gradual diminution in the number of corpuscles, which often becomes more accentuated toward the end of the fever,* the most marked anæmia being reached at about the beginning of convalescence. The recovery from this anæmia has been in most instances rather slow.† The hæmoglobin falls with the corpuscles, but usually to a somewhat greater extent. The colorless corpuscles, which at the beginning are about normal in number, fall gradually during the fever, reaching a slightly subnormal number and returning to the normal point again with convalescence. We have not noticed in our cases the slight leucocytosis at the beginning of convalescence which Bonne believes to be the rule. It should be remembered that intercurrent inflammatory processes, as well as certain methods of treatment, may have a marked influence on the proportion of leucocytes in the blood. Cold baths, for instance, have been shown by Winternitz[50] and the writer[51] to be followed by a decided temporary increase in the number of colorless corpuscles. It is perhaps more probable that this increase in the leucocytes after cold bathing is the result of local conditions on the surface of the body, whence the blood for examination is obtained, rather than that it is a true leucocytosis. We have never seen any large white elements containing red blood corpuscles as described by Eichorst.[24] In most of the cases which we have observed, the degree of anæmia following typhoid fever has been but slight, an observation agreeing with those of the majority of the above-mentioned authors. Few of these observers have, however, laid stress on the fact that this post-typhoid anæmia may be severe enough to form of itself a grave complication of typhoid fever, and for this reason the two following cases may be of interest.

* It is not impossible that the suddenness of the fall may depend to some extent on the presence or absence in the earlier stages of diarrhœa or sweating, which might, through the resulting concentration of the blood, mask temporarily the first corpuscular losses.

† We do not refer here to the grave anæmia which may be produced by certain drugs such as pyrodin (Lafleur[44]). Our observations have been wholly on cases which have been treated entirely by the cold bath.

Case 1. C. C., single, aged 30, a native of Italy, was admitted to the Johns Hopkins Hospital on November 17, 1890. He was a fireman on a steamer and had been but seven days in Baltimore, whither he had come from Port Antonio, Cuba. He spoke but little English and the history was not as full as could be wished.

The family history was good so far as could be made out, and the patient asserted that he had always been healthy and strong.

The illness of which he then complained began quite sharply seven days before entrance, with headache, general pains and feverish sensations. There was no cough, no nose-bleed, no vomiting, no actual abdominal pain, though he complained of a "heavy feeling" in the abdomen and an aching pain in his back and legs. There was anorexia and at times nausea.

Present condition. On entrance he was found to be an able-bodied man. The lips and mucous membranes were of good color. The face and upper part of the thorax were flushed; the conjunctivæ injected. The tongue showed a thin brownish fur; edges clean and indented. The temperature on admission was 104.5°, and rose later in the afternoon to 106°; pulse 96, dicrotic; respiration 30. The lungs were everywhere resonant; the heart sounds were clear and normal; possibly a very faint systolic murmur at the base; cardiac impulse normal.

The abdomen was not distended, and showed no eruption beyond a rose-red papule in the epigastrium and two rather deep-colored papules on the left side. There was slight tenderness in the right iliac fossa. Hepatic flatness extended from the sixth rib to the costal margin. Edge of the spleen palpable, soft, not sharp; splenic flatness from the ninth to the lower border of the eleventh rib to the costal margin. The pillars of the fauces and pharynx were somewhat swollen and congested. The blood showed no malarial organisms. A liquid diet was ordered, 180 cc. of milk or broth every two hours, and tub-baths at 70° every three hours if the rectal temperature was above 102.5°. From the 18th to the 21st the temperature ranged between 98.2° and 105.4°. The fall of temperature after the baths was in many instances very marked, on one occasion amounting to nearly six degrees.

November 22nd.—The temperature during the past 24 hours has risen as high as 105°; the patient has had four baths; is a little nervous, not delirious; pulse 130, not so dicrotic; no fresh typhoid eruption.

November 23rd.—The patient is quite rational; tongue a little dry; slight lividity of surface; fever tends to reach 104.5° between the baths; pulse 96 to 120, quite compressible, distinctly dicrotic. Cardiac sounds very faint at apex, the first sound being especially weak. Breathing clear at the bases, no râles; has been having 180 cc. of whiskey during the twenty-four hours, against which he rebels. Port wine, 350 cc. in the twenty-four hours.

November 24th.—The pulse is soft and compressible; it has lost its dicrotic character entirely. Superficial veins dilated; no definite rash; heart sounds feeble. Patient has had diarrhœa ever since entrance; has now about five liquid stools a day.

November 25th.—Delirious; involuntary micturition and defæcation.

November 28th.—Patient seems a trifle better; pulse 108, dicrotic, occasionally dropping a beat. Heart sounds feeble; no murmur. *Urine* clear, acid, 1013, trace of albumin, numerous hyaline and finely granular casts; epithelium and mucous cylindroids; diazo reaction present.

November 30th.—The temperature has fallen somewhat; patient, however, seems very feeble, though he is quite conscious. The bases of the lungs are clear.

December 1st.—The pulse is feeble; there is some subsultus; patient is rational but drowsy; the diarrhœa has entirely disappeared. The patient is very anæmic.

From this time on the fever diminished; the temperature on December 2nd touched a normal point. The anæmia, however, appeared to increase in intensity. The patient was of a waxy pallor, and the throbbing of the carotids was striking.

From the 5th to the 20th the temperature was most of the time above 99°, touching a point between 100° and 101° daily, occasionally above 101°. The patient was extremely anæmic and very feeble.

December 16th.—Splenic dulness extends from the eighth rib to the lower border of the tenth. The patient is profoundly anæmic.

December 21st.—Urine free from albumin. The patient slowly improved, without further interruption, excepting for a slight febrile attack between the 6th and 10th of January, for which no cause could be found. The spleen remained enlarged and the anæmia was very marked, and it was not until the 20th of January that the patient was allowed to get out of bed. This was followed by dizzi-

ness and marked œdema of the legs, and after about five days the patient was put to bed again. Again on the 13th of February he was allowed to sit up, but even at this time he still developed considerable œdema of the legs. From this time on, however, he made a satisfactory improvement. At the time of his discharge, March 13th, the patient considered himself well, though he was still somewhat pale. He had gained 28½ pounds.

While on entrance the patient presented the appearance of a man with at least a normal condition of his blood, by the time he had been in the hospital for two or three weeks he began to show evidences of marked anæmia. The blood, counted for the first time on December 11th, the thirty-first day of his disease, showed red corpuscles 1,996,000; colorless corpuscles 5,500. The accompanying chart shows the blood-counts and estimations of hæmoglobin that were made during the patient's stay in hospital. The count was unfortunately not made on entrance, but it is safe to say that the number of corpuscles must have been normal, as the patient was a strong, large man with a very full color. The appearance also of the dried specimens was sufficient evidence that the blood was in a normal condition.

The following examinations of the blood were made:

The Thoma-Zeiss blood-counter and the von Fleischl hæmometer were used. In counting the blood, the whole or one-half of one field* of blood in the Thoma-Zeiss instrument was counted for the corpuscles, the cell washed, and the same process repeated from one to three times more, the mean of the counts being taken. At least four whole fields of the blood-counter were always counted for the colorless corpuscles. Where the number of the colorless corpuscles was relatively constant, the mean of the four fields was taken; otherwise five or six, or in several instances seven fields were counted. In this way a fair estimate was probably obtained of both varieties of corpuscles. Toison's solution† was used to dilute the blood. The dilution was usually 1 to 200. Dried cover-glass specimens were examined after the method of Ehrlich.[28] These were first heated for from one to

* By this is understood the whole 400 squares.

† Sodii chloridi ..... 1.
Sodii sulphatis ..... 8.
Glycerini pur. (neutral at 30° C.) ..... 30.
Aquæ ..... 160.
Methyl violet 5B 0.025

Methyl violet from Merck's or Grubler's laboratories gives good results.

two hours on a copper plate, at a temperature between 100° and 120° C. They were for the most part stained with the triple stain of acid fuchsin, methyl green and orange *G*. In other instances eosin and methylene blue, or a stain of eosin, nigrosin and aurantia in glycerine were used. Differential counts of the leucocytes were made upon a movable stage of Zeiss's construction. The Zeiss $\frac{1}{12}$ oil immersion lens was used, and eyepieces Nos. 2 and 4.

On November 19th, approximately the tenth day of the disease, the examination of stained specimens showed an essentially normal blood. The red corpuscles were natural in appearance, showing no undue variation in size, shape, or staining propensities. The differential count of 1000 leucocytes showed:

Lymphocytes*	8.7 per cent.
Large mononuclear leucocytes	22.5 " "
Transitional forms	1. " "
"Multinuclear" neutrophilic leucocytes	66. " "
Eosinophiles	1.8 " "

In these differential counts the leucocytes were divided according to Ehrlich's classification, which he gives in the Charité Annalen, 12 Jahrgang.

(1) Lymphocytes, small cells approaching the red corpuscles in size, the body of which is filled with a large, round, deeply staining nucleus, while the protoplasm is represented by a small ring about the nucleus.

(2) Mononuclear leucocytes, larger cells which have a relatively large oval or ovoid, less deeply staining nucleus, and a relatively large amount of protoplasm.

(3) Transitional forms, cells of a similar appearance to the foregoing, which differ from them only in that the nucleus shows certain indentations which may give it the appearance of an hour-glass.

(4) The so-called "multinuclear"† elements, which are perhaps a

* It would be more correct to call this first class "small mononuclear leucocytes[49]," as it includes some small transparent forms. I have decided, however, to publish the counts and remarks just as they appear in my notes.

† The terms "multinuclear" and "polynuclear" are incorrect, as the nucleus is really single, though polymorphous. In Germany the term "polymorphkernige leucocyten" is common and much better, and we should be more correct if we used in English some such term as *poikilonuclear*, in the absence of a better translation. It is a question, however, whether it is advisable to add any more terms to those now existing in the classification of the various formed elements of the blood, and it seems, on the whole, best to continue at present using the terms "multi-" and "polynuclear," protesting at the same time against their inaccuracy.

trifle smaller than the large mononuclear, and show the characteristic polymorphous nucleus. These cells contain a thick, neutrophilic granulation.

(5) Eosinophilic leucocytes, similar cells, usually "multinuclear," containing the larger and more refractive eosinophilic granules. As a general thing, the protoplasm of the lymphocytes takes with the triple stain a red violet color, while that of the large mononuclear elements has but a slight affinity for coloring matters. There exist, however, in all bloods, a number of mononuclear and some "multinuclear" elements, which have a protoplasm which remains entirely unstained, looking like a white spot or small vacuole in the middle of the stained specimen. By far the greater part of these elements were included under the large mononuclear leucocytes in these counts, though it must be said that a certain distinct though small proportion were considered in the class of lymphocytes. In this first count a very considerable number of the large mononuclear leucocytes and a few of those classed under the head of lymphocytes showed a perfectly hyaline, transparent protoplasm. From this time until the 11th of December, no examination of the blood was made. It had been noticed for some little time that the patient had been developing a marked anæmia.

December 11th, thirty-second day of the disease.—Red corpuscles, 1,996,000; colorless corpuscles, 5,500; no estimation of the hæmoglobin.

December 15th, thirty-sixth day.—Specimens of blood stained with the triple stain showed some difference in the size of the red corpuscles; no marked poikilocytosis. The leucocytes appeared to be present in a slightly subnormal, or at all events not an increased number. Differential count:

Lymphocytes	20.6 per cent.
Large mononuclear leucocytes	15.4 " "
Transitional forms	2.0 " "
"Multinuclear" neutrophiles	52.2 " "
Eosinophiles	9.8 " "

A considerable number of mononuclear leucocytes with transparent protoplasm were seen. As before, however, the majority were classed under the head of large mononuclear leucocytes, some in the column of lymphocytes. Occasional small leucocytes with transparent protoplasm and polymorphous nuclei were seen.

December 18th, thirty-ninth day.—Red corpuscles, 2,140,000; colorless corpuscles, 4,000; hæmoglobin not estimated. The stained specimens showed the same condition as on the last examination; the specimens were not so good. There were numerous distorted and broken leucocytes on the cover-glasses, which appeared to be mainly large mononuclear elements. The differential count, which was therefore not so reliable, showed:

Lymphocytes	19.4 per cent.
Large mononuclear leucocytes	10.3 " "
Transitional forms	2.7 " "
"Multinuclear" neutrophiles	54.5 " "
Eosinophiles	12.8 " "

Two nucleated red corpuscles of the normoblastic (Ehrlich) type were noted. From this time on no further differential counts were made until the day of discharge. During the next several weeks numerous stained specimens were made, and for a short time after this the nucleated red corpuscles were found to be more numerous. They were always of the normoblastic type.

December 29th.—Red corpuscles, 2,464,000; colorless corpuscles, 5,000.

January 8th.—Red corpuscles, 2,424,000; colorless corpuscles, 4,000; hæmoglobin, 32 per cent.

January 15th.—Red corpuscles, 3,551,000; colorless corpuscles, 7,000; hæmoglobin, 56 per cent.

January 26th.—The patient has been sitting up and walking about for several days. There has been œdema of the feet. Red corpuscles, 3,152,000; colorless corpuscles, 10,000; hæmoglobin, 47 per cent.

February 9th.—The patient has been kept in bed since last entry. Red corpuscles, 3,897,000; colorless corpuscles, 8,000; hæmoglobin, 56 per cent.

February 25th.—The patient has been up and about for a week or ten days. Red corpuscles, 3,325,000; colorless corpuscles, 4,500; hæmoglobin, 59 per cent.

March 13th.—The patient was discharged to-day, 123 days after the beginning of his illness. Red corpuscles, 4,604,000; colorless corpuscles, 9,000; hæmoglobin, 70 per cent. The stained

specimens showed essentially a normal blood. The differential count showed:

Lymphocytes	13.2 per cent.
Large mononuclear leucocytes	2.7 " "
Transitional forms	1.0 " "
"Multinuclear" neutrophiles	70.4 " "
Eosinophiles	12.7 " "

Case 2. E. H., aged 25, fireman, was admitted to the Johns Hopkins Hospital on the 17th of December, 1890, complaining of fever, headache and general pains.

Family history. Father and mother living and well; the patient knows of no hereditary disease in his family.

Personal history. He has always been in good health excepting for an attack of pneumonia and "acute gastritis" about eight years ago. About a week ago he suddenly began to complain of feverishness and chilly sensations, severe headache, pains in the limbs and back, and some abdominal pain. The bowels have been constipated; no bleeding from the nose; slight cough at times. Has not worked for a week.

On admission to the hospital he was quite rational and answered questions promptly, but at times during the rest of the day he was somewhat delirious.

December 18th.—Present condition: Sunburned, flushed, eyes bright, pupils normal; tongue dry and brown in the middle. Temperature on admission 100°; pulse 108, dicrotic; respiration 48. Lungs clear on percussion, now and then a sibilant râle is heard on auscultation. Heart sounds clear at apex and base. Abdomen full, tympanitic, no rash. Spleen not distinctly palpable. Some tenderness in the upper part of the right iliac region. The blood showed no malarial organisms. Urine high-colored, acid, trace of albumin; diazo reaction well marked. A liquid diet was ordered, milk and broths, 180 cc., every two hours; tub-baths at 70° every three hours when the rectal temperature was above 102.5°.

December 20th.—The temperature has ranged between 100° and 105.4.° The falls in temperature after the baths have been moderate. Has had nine baths. The abdomen is soft, no rose spots; spleen not palpable; urine acid, specific gravity 1010, trace of albumin; diazo reaction not so marked.

The temperature after the 20th gradually fell, on the 26th between 8 a. m. and 8 p. m. touching no point higher than 100.8°, and on the 28th being under 100°. The general condition of the patient improved on the whole, excepting for a very marked and rapidly developing anæmia. From the 31st of December throughout January the temperature touched nearly every day a point above 101°, and at times above 102°, while occasionally it would reach a point as low as 97° or 98°.

On the 10th of January the patient was profoundly anæmic; skin of a waxy pallor; pulse very soft, carotids throbbing. Fowler's solution was ordered, ♏iii, three times a day. This was increased to ♏iv on the 14th. On the 22nd of January the edge of the spleen was to be made out 4 cm. below the costal margin. The patient has been improving in many ways and the diet has been materially increased, but the grave anæmia still remains and the patient is very feeble.

From the 5th of February to the 20th the temperature ranged between 97.4° and 100.6°, rarely reaching a point as high as 100.5°. On the 13th the patient, though still very anæmic, was allowed to sit up out of bed.

February 21st.—Patient had yesterday a slight chill, at noon the temperature rising to 103.2° and remaining elevated throughout the day. The spleen is still enlarged. The blood shows no malarial organisms, no leucocytosis. The temperature to-day is normal.

February 23rd.—Temperature was normal on the 21st from 8 a. m. to 12 m., when it began to rise, and at 6 p. m. was 102°. This was followed by sweating; no actual chill. Temperature fell to 97.2° at 8 a. m. No pain, no cough or expectoration; no rose spots visible. Abdomen full, not tense. From this time on the temperature was practically normal. After a few days' rest in bed the patient was allowed to sit up again and made an uninterrupted recovery, leaving the hospital well on the 14th of March, the 95th day after the beginning of his disease.

Though the condition of the blood was greatly improved, the anæmia was still somewhat marked on his discharge.

Examination of the Blood.

December 17th.—On the day of entrance, apparently about the seventh day of the disease, dried and stained specimens of the blood

were examined. The red corpuscles showed nothing abnormal in size or shape; no poikilocytosis. The leucocytes appeared to be about normal in number. The differential count of 1000 leucocytes showed:

Lymphocytes	11.3 per cent.
Large mononuclear leucocytes	11. " "
Transitional forms	.3 " "
"Multinuclear" neutrophiles	73.2 " "
Eosinophiles	4.2 " "

December 19th, ninth day of the disease.—Red corpuscles, 4,092,000; colorless corpuscles, 5,500.

December 26th, sixteenth day of the disease.—Red corpuscles, 2,226,000; colorless corpuscles, 6,800.

January 6th, twenty-seventh day.—Red corpuscles, 1,426,000; colorless corpuscles, 8,000; hæmoglobin, 24 per cent. Dried and stained specimens showed a marked pallor of the red corpuscles and considerable difference in size, though there was no great poikilocytosis. A few nucleated red corpuscles (normoblasts) were found. While making a differential count of 1000 leucocytes two normoblasts were seen. The differential count of 1000 leucocytes showed:

Lymphocytes	18.1 per cent.
Large mononuclear leucocytes	22.4 " "
Transitional forms	4.5 " "
"Multinuclear" neutrophiles	53.1 " "
Eosinophiles	1.9 " "

A large number of mononuclear leucocytes with almost transparent protoplasm were noticed here as in the specimens of blood in Case I. Specimens stained with eosin and methylene blue showed considerable numbers of red corpuscles taking a diffuse stain, "degenerate forms" (Ehrlich), "polychromatophilic corpuscles" (Gabritchewsky[45]).

January 14th, thirty-fifth day.—Red corpuscles, 1,352,666; colorless corpuscles, 6,500; hæmoglobin, 27.5 per cent.

January 24th, forty-fifth day.—Red corpuscles, 1,648,666; colorless corpuscles, 7,000; hæmoglobin, 28 per cent. Stained specimens showed, as in the last specimen, a considerable difference in the size of individual red corpuscles; no great poikilocytosis. Numerous

polychromatophilic corpuscles. A considerable number of large transparent mononuclear leucocytes, and also a good many which were small and were classed with the lymphocytes. Nucleated red corpuscles (normoblasts) were numerous; six were seen while counting 1000 leucocytes. The differential count showed:

Lymphocytes	23.7 per cent.
Large mononuclear leucocytes	29.8 " "
Transitional forms	4.6 " "
"Multinuclear" neutrophiles	37.3 " "
Eosinophiles	4.6 " "

January 31st, fifty-second day.—Red corpuscles, 2,234,000; colorless corpuscles, 8,000; hæmoglobin, 37.5 per cent.

February 9th, sixticth day.—Red corpuscles, 2,314,000; colorless corpuscles, 2,000; hæmoglobin, 37.5 per cent.

February 20th, seventy-first day.—Red corpuscles, 2,109,333; colorless corpuscles, 2,000; hæmoglobin not estimated.

February 26th, seventy-seventh day.—Dried specimens examined showed no leucocytosis, considerable difference in the size of the corpuscles, but scarcely as much as on the last examination. A considerable number of nucleated red corpuscles were seen. The differential count of the leucocytes showed:

Lymphocytes	23.9 per cent.
Large mononuclear leucocytes	11.2 " "
Transitional forms	4.2 " "
"Multinuclear" neutrophiles	58.8 " "
Eosinophiles	1.7 " "
Myelocytes	0.2 " "

The most marked change in this specimen was the appreciably smaller number of transparent leucocytes. Two mononuclear leucocytes with neutrophilic granules were seen. The nucleus, however, was not very large.

March 10th, ninetieth day.—Red corpuscles, 3,757,000; colorless corpuscles, 9,333; hæmoglobin, 52.5 per cent.

March 14th, ninety-fourth day.—Red corpuscles, 4,096,000; colorless corpuscles, 8,000; hæmoglobin, 66 per cent. Dried specimens were made on this day, but were unfortunately lost.

A glance at the appended charts * shows that in Case I a man who must have had a normal blood on entrance, showed a fall of over 3,000,000 on the 31st day of the disease. Whether this represented really the lowest point, or whether during the week before it had been yet lower, one cannot say. The patient was at this time practically afebrile; the fever he had after this was in all probability the fever of anæmia. Three months afterwards, at the time of the discharge, the blood had not yet reached its normal condition.

In Case II the fall in the number of red corpuscles had already begun on the tenth day of the disease, the number of red corpuscles being 4,092,000, a loss of at least 1,000,000. In the next seven days, during the second and third weeks, before the temperature had reached the normal point, there was a loss of 1,866,000 corpuscles. This fall continued during the next nineteen days, during which time the patient lost 94,400 corpuscles to the cubic millimetre. The lowest point occurred when the patient was probably free from his disease, the fever present at that time being probably the fever of anæmia. In this case, then, we see a gradual fall in the number of red corpuscles from the beginning, which was accentuated toward the latter part of the febrile period; the fall extended into the period of the beginning of convalescence. The curve is thus similar to that described by the majority of observers who have been mentioned above, while it corresponds entirely with our observations in cases where the loss of corpuscles was slight and unimportant. On the ninety-fourth day after the beginning of the disease the blood had not yet reached the normal point.

The hæmoglobin in both cases was diminished in greater proportion than the number of the corpuscles.

* Before commenting on the charts it may be well to state what we consider to be the normal number of red and colorless corpuscles to the cubic millimetre of blood. There are marked variances between the results of different observers, depending probably on slight differences in instruments and technique, and oftentimes a consideration of the individual standard of each observer will assist considerably in elucidating the results. From the counts made in Prof. Osler's clinic by Dr. J. S. Billings, Jr., and the writer, we are inclined to place the normal number of red corpuscles between 5 and 6,000,000, with the mean nearer 5,500,000 than it is to 5,000,000, while the mean normal number of leucocytes we have found to be not far from 7,000 to the cmm. A discussion of this whole question, with an interesting table showing the changes in the number of red and colorless corpuscles in a healthy individual at different times of the day, will be found in the work of Reinert.[46]

BLOOD CHARTS.

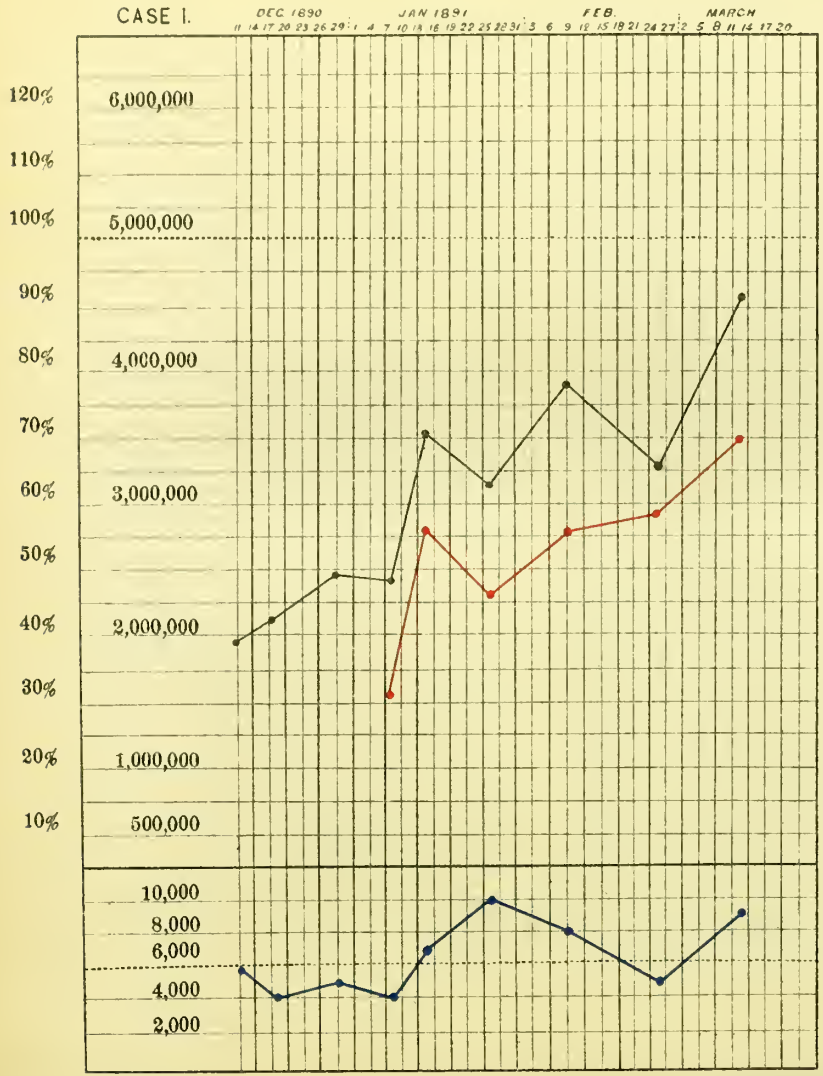
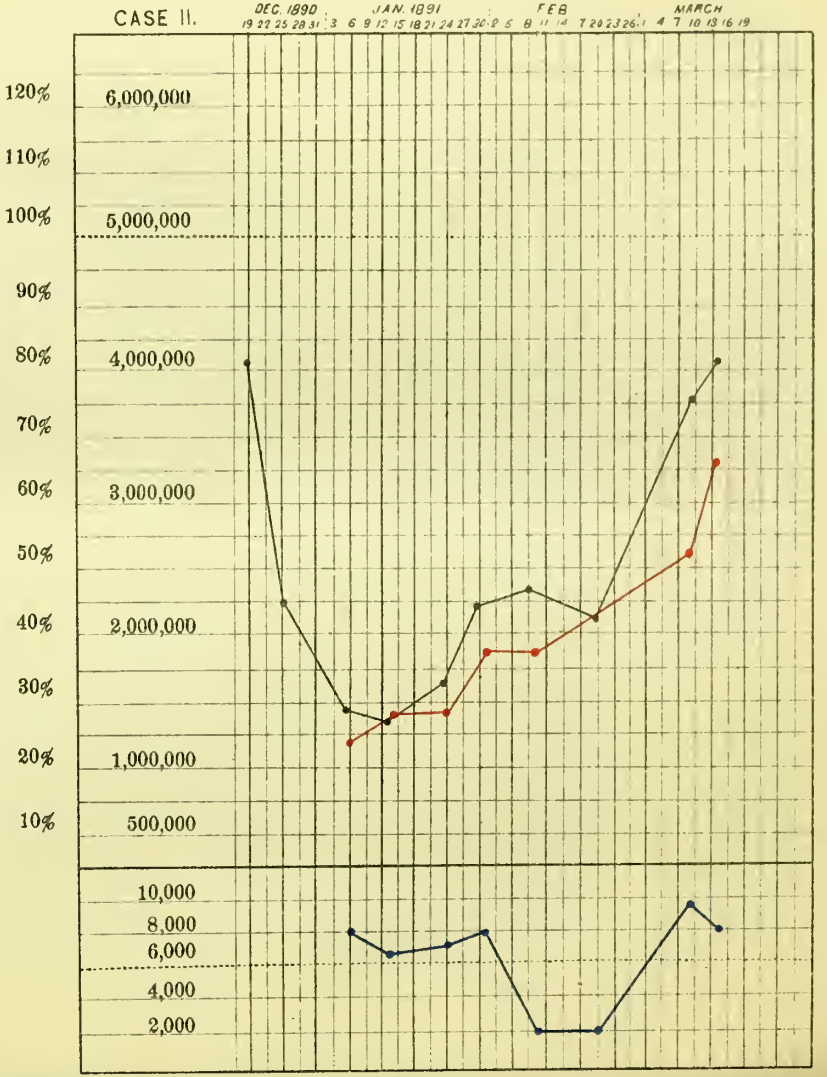


Chart IV.



BLACK —RED CORPUSCLES.

Chart V.

The colorless corpuscles were found in Case I to have been somewhat subnormal during the first part of convalescence, and to have been a trifle higher, though still close to the normal point during the latter part. The dried specimens examined at the beginning of the process left little doubt that the number was normal or subnormal at that time. In Case II during the febrile period two counts showed about a normal or slightly subnormal number. During the greater part of convalescence the number was close to the normal point, tending toward the end, in the last two counts, to be a trifle higher.

The picture, then, which one obtains from the charts is that of an ordinary secondary anæmia, barring the rather unusually small number of the colorless corpuscles, a fact which was probably due to the typhoid fever itself, and may be found to be somewhat characteristic of these anæmiæ, as most acute secondary anæmiæ are associated with a slight leucocytosis. On referring, however, to the differential counts of the colorless corpuscles which were made in the dried and stained specimens, we find another condition which is somewhat at variance with that which is commonly observed in a secondary anæmia. Here we usually expect to find a relative increase in the multinuclear neutrophiles at the expense of the small mononuclear elements (lymphocytes, small transparent forms). Under normal circumstances counts show from 15 to 25 per cent. of small mononuclear elements, about 6 per cent., more or less, of large mononuclear and transitional forms, about 70 to 75 per cent. of "multinuclear" neutrophiles, and 2 to 5 per cent. of eosinophiles. We note, however, in these counts, that while the small mononuclear elements remain in most instances about normal in number, the large mononuclear leucocytes are very markedly increased, while the "multinuclear" neutrophiles show invariably a diminution. In only one of these counts does the condition of the blood approach the normal: the final count in Case I. Here, however, we see a slight relative diminution of the lymphocytes with an increase in the number of "multinuclear" elements (neutrophiles and eosinophiles), a fact which is accounted for by the slight leucocytosis, 9,000. This condition of the blood, a diminution in the "multinuclear" neutrophiles with a relative increase in the large mononuclear and transitional elements, has been shown by Ouskow[43] and Khetagurow[46] in a number of careful observations to be a

characteristic point during the course of typhoid fever. Ouskow has made a much more minute classification of the leucocytes than that originally proposed by Ehrlich, and this very minute classification he resolves again into three classes, which he calls (1) the young elements, (2) the ripe elements, and (3) the over-ripe elements. In the young elements he includes the typical lymphocytes of Ehrlich, the small bodies a little smaller or a little larger than red corpuscles with deeply staining protoplasm, and a nucleus which likewise has a strong affinity for coloring matters, and almost entirely fills the corpuscles. He also includes in the young elements bodies which are somewhat larger than these lymphocytes, which have a round nucleus resembling in size those of the lymphocytes, but taking a somewhat paler stain, and showing a greater quantity of protoplasm which is usually but very faintly colored or entirely transparent. Under the class of ripe elements he includes the large mononuclear leucocytes with transparent or with slightly colored protoplasm, and the so-called transitional* forms (Uebergangformen) of Ehrlich; while under the over-ripe elements he includes the multinuclear neutrophiles and the eosinophiles. He believes that the multinuclear neutrophiles develop in common from both the varieties of young elements, the typical lymphocytes, and the small transparent corpuscles, the lymphocytes coming from the lymphatic apparatus, the lymph glands, the Malpighian bodies of the spleen, the small transparent corpuscles coming in great part from the bone-marrow.† He

*By the term "transitional forms" Ouskow and his pupils designate an entirely different variety of leucocytes from that to which Ehrlich originally gave the name. Considering all the varieties of leucocytes with which we meet in the blood to be simply different stages in the development of one cell, Ouskow has given the name "transitional forms" to that variety of large mononuclear leucocytes, the protoplasm of which shows some affinity for coloring matters, in contradistinction to the "transparent forms"; it is a transitional stage between the other mononuclear leucocytes and the "multinuclear" neutrophiles. Ehrlich's transitional form is simply one step further; it is the large mononuclear element which already shows indentations in its nucleus, evidences of its transition to a more polymorphous condition. Ehrlich has not apparently considered it a proven fact that the lymphocytes do actually develop into "multinuclear" neutrophiles. The term "transitional form" when used in this paper should *always be understood in the sense of Ehrlich.*

†The explanation of the fact that from smear preparations from the spleen we always find so large a number of large mononuclear leucocytes may be, as Emelianow[52] suggests, namely, that the meshes of the spleen form, as it were, a hotbed in which the growth from the small to the large mononuclear forms takes place.

finds under normal circumstances about 18 per cent. of young elements, 6 per cent. of ripe elements, and 75 per cent. of over-ripe elements present in the blood. In a careful series of observations started by Ouskow and continued by Khetagurow, it has been shown that during typhoid fever (1) there is a sharp falling off in the relative number of "multinuclear" elements which may represent less than 50 per cent. of the total number of leucocytes; (2) this fall begins usually in the first week, but is more sharply expressed in the second or third, or even fourth week; (3) the percentage of over-ripe elements begins to increase about three to twelve days after the disappearance of the fever; Khetagurow finds that it does not reach the normal point until the tenth or eleventh week; (4) the proportion of the small mononuclear elements to the large mononuclear and transitional forms is usually about as $1\frac{1}{2} : 1$, instead of being as is normal about as $3 : 1$; (5) the decrease in the number of multinuclear elements depends not so much on a parallel increase in the percentage of the small mononuclear elements, as on the increase in the percentage of the large mononuclear cells.

The varieties of leucocytes, however, which these authors found to be particularly increased—observations which the writer has been able to verify—are the transparent and faintly staining mononuclear leucocytes, which closely border upon the line separating the small mononuclear (young) from the large mononuclear (ripe) elements; they are included for the most part among the large mononuclear (ripe) elements. It is this point which will make, and has made in some of our cases, considerable variations in individual records, between the proportion of young and ripe elements. In some instances, as in the first count in Case I, a number of corpuscles which probably should have gone into the class of small mononuclear elements, were classed as large mononuclear,* the class

*As these different forms are probably simply different stages of development—a gradual growth—it is hard to draw an exact line in such necessarily artificial divisions as these. The writer generally observes the following rule: where the nucleus of a mononuclear element is similar in size and shape to those of the lymphocytes, even though the affinity for coloring matters be less, the cell is classified under the small mononuclear elements, until the size of the cell as a whole passes that of the ordinary "multinuclear" neutrophile. Thus to a certain extent more attention is paid to the nucleus than to the cell body as a whole. Some cells, no larger than the largest of those which are classed under small mononuclear leucocytes, may be at times classed under large mononuclear elements, because of their larger, more ovoid, paler nucleus. At the time when these counts were made the writer had no such fixed rule.

of "lymphocytes" being mainly restricted to the true lymphocytes. All these differential counts were made before the author was familiar with the work of Ouskow or Khetagurow, and it is interesting to note how thoroughly confirmatory they are of the work of these two observers; the increase in mononuclear leucocytes and the decrease in multinuclear were noted in each case and commented upon. We have been able further, in a considerable number of cases, to entirely corroborate these observations, and while these changes in the proportion of the different varieties of leucocytes may not be pathognomonic of typhoid fever, they form quite a characteristic point, distinguishing the blood of typhoid fever from that of most of the other febrile processes with which it is likely to be confounded. A majority of these conditions are inflammatory in nature, and all show at least a normal, and usually a considerably increased number of "multinuclear" neutrophilic elements, with a relative diminution in the small mononuclear. These points alone, the small number of leucocytes and the changed relative proportion of the different varieties, are the distinguishing features of these two cases of post-typhoid anæmia from a hæmatological standpoint.

Another interesting point in the blood of each of these patients, particularly in Case I, is the relatively large proportion of eosinophiles. In all other cases of typhoid fever in which the writer has had occasion to examine the blood, eosinophiles have been present in a very small percentage, if indeed they were found at all.

The causes of so grave an anæmia as occurred in these two cases are not easy to appreciate. Leichtenstern and Zaeslein, as has been mentioned above, are inclined to ascribe the anæmia largely to a dilution of the blood, while Hayem on the other hand is more inclined to assume that it is the result of a definite destruction of the corpuscles; the corpuscles which have resisted the high fever during several weeks, finally give way in considerable numbers. It is not impossible, considering the observations of Leichtenstern and Zaeslein, that an actual dilution of the blood may occur, but there can be no doubt, after the examination of the blood in such cases as these two, in either fresh or dried and stained specimens, that a very severe actual anæmia exists (changes in the size and shape of the red discs —nucleated red corpuscles). In both of these instances, after the disappearance of the toxic symptoms, the condition was such as to cause grave apprehension, the patients showing all the physical symptoms

of an extremely severe anæmia, while the examinations of the blood, as has been said, can leave no doubt that an actual anæmia existed. The length of the fever alone is probably insufficient to account for such anæmia as this. In neither case was the fever of remarkably long duration. The first case was one of more than usual severity and was associated with considerable diarrhœa. In Case II, however, where the anæmia was graver, the case was regarded as rather mild. The symptoms during the fever were at no time alarming, and the temperature reached practically a normal point on the nineteenth or twentieth day; the fever on the days following was probably the fever of anæmia. Most of the very severe cases, no matter whether they resulted fatally or not, in which the blood was examined, showed a relatively slight anæmia. The patient, for instance, in the next bed to that occupied by Case II passed through an extremely severe attack of typhoid fever, which lasted 93 days; at one time the patient was almost pulseless, and yet the lowest point to which the red corpuscles sank was 4,434,000. This patient entered the hospital two days after Case II, and left perfectly well fourteen days before. It is not improbable that an actual anæmia in these cases is due to the direct destruction of the red corpuscles by the toxine which produces the symptoms, but it is hard to understand why, in the case of a robust man with an apparently mild infection and no untoward symptoms, the red corpuscles should fall to 1,352,000 per cubic millimetre, while in that of his neighbor, a much less vigorous-looking man, with a most severe attack, the red corpuscles should never have fallen below 4,434,000. It is not impossible that there may be in some cases a dilution of the blood as a whole, which may affect the blood-count, but it is hard to believe that this is the important element in most cases.

The importance of such cases as these cannot be overlooked. A patient with this degree of anæmia would be assuredly much more liable to complications and secondary infections, of which, possibly, the case reported by Ernesti[17] is an example, while the danger of sudden death from syncope would certainly suggest itself. Out of 2000 fatal cases of typhoid fever occurring at the General Hospital in Munich, Hölscher[48] found 54 cases, or 2.7 per cent., which showed a marked general anæmia.

With regard to the treatment of such cases as these there is little to say. There is apparently no reason for deviation from the meas-

ures usually adopted in any grave secondary anæmia. In both instances the patients were given iron in the form of Blaud's pills, and in the more severe case arsenic (liq. kali arsenitis) was added. In relation to one point, however, these cases are instructive. The importance of rest in bed in the treatment of grave anæmia is emphasized in an interesting manner by the blood charts of both patients, particularly by that of Case I. Here we see that on January 15, 1891, the blood-count showed 3,551,000 red corpuscles to the cmm.; while on the 26th, after having been out of bed for several days, the patient had developed œdema of the dependent parts, and the blood-count showed a loss of nearly 400,000 red corpuscles per cmm. After two weeks' rest in bed there was a rise of 745,000, while again, a week after leaving bed the second time, there was a loss of over 500,000 red corpuscles.

In Case II the chart shows on February 9, 1891, 2,314,000 red corpuscles, but eleven days later, after the patient had been out of bed a week, the count showed a loss of over 200,000. The writer has observed a similar curve in a case of pernicious anæmia which was improving under treatment. There is surely no reason to ascribe such changes to a mere dilution of the blood; in both instances the patient had been on a full diet a long time before leaving his bed. This point—the importance of rest in bed in the treatment of grave anæmia—has been, perhaps, hardly emphasized enough by most writers. In many of the more severe cases of chlorosis, for instance, cases where there is an actual corpuscular anæmia, an initiation of the treatment by a week or ten days' confinement to bed would probably materially hasten convalescence.

Remarks on the Value of the Examination of the Blood in Typhoid Fever.

From the results of the examinations of the blood made by the observers who have already been quoted, and from a considerable number of observations which we have been able to make ourselves, the following may be said in summary to be the more important changes occurring in the blood in typhoid fever.

Red corpuscles. At the beginning of the fever the number of red corpuscles is usually normal, and often at the upper limit of normal, for the reason that the patients are usually young and strong individuals, while in some instances an initial diarrhœa may cause some

concentration of the blood. During the first weeks the number of corpuscles, with some fluctuation, falls gradually, but usually to a relatively slight extent. With defervescence there is, however, a more rapid fall in the number of red corpuscles, continuing often into and reaching its lowest point usually about the first week of convalescence. Recovery from this anæmia is generally rather gradual. From cases in Prof. Osler's clinic, where careful blood-counts* were made during the fever, the following table may be made:

First week.	Second week.	Third week.	Fourth week.	Fifth week.	Sixth week.
2 counts	10 counts	9 counts	6 counts	7 counts	4 counts
5,636,000	4,960,599	4,951,535	4,038,333	3,856,786	4,364,250

The counts made after this show a gradual increase, but are too scattering to classify.

The averages in these few instances are somewhat low because of the inclusion of the two severe cases above recorded. Ordinarily, the fall in the number of red corpuscles is relatively slight, and as a rule bears a direct relation to the severity of the case, but at times a grave anæmia may follow an apparently mild case of the disease, as shown in Case II. The anæmia may be severe enough to form of itself a dangerous complication of the process.

Hæmoglobin. The hæmoglobin falls always with the red corpuscles; the loss, however, is relatively greater than the corpuscular loss, and the return of the curve to normal is further delayed. The observations which I have recorded in thirteen cases are not numerous enough to make a table of any value. They agree, however, entirely with the preceding statement.

Leucocytes. The number of leucocytes in the cubic millimetre at the beginning of the fever is about normal, but tends throughout the course to diminish, reaching its lowest point toward the end of defervescence. With the beginning of convalescence begins the return to normal, which may last several weeks. This gradual fall is well shown in the following table taken from over 200 counts made by Dr. J. S. Billings, Jr., and myself:†

First week.	Second week.	Third week.	Fourth week.	Fifth week.	Sixth week.
22 counts	50 counts	41 counts	28 counts	16 counts	5 counts
7,212	6,468	6,351	5,877	6,621	7,000

* I am indebted to Dr. J. S. Billings, Jr., for several of these counts.

†All counts made directly after baths were omitted.

After this the blood-counts are too scattered to make a reliable table, but they show about a normal mean. It should be said, however, that this table includes one case in which two counts were made, one in the first and one in the third week, both of which were unusually high; and as this is one of the earliest cases, it is not impossible that the counts may have been made shortly after baths, though it was not noted on the record. If we omit this case we have a table which is probably more correct:

First week.	Second week.	Third week.	Fourth week.	Fifth week.	Sixth week.
21 counts	50 counts	40 counts	28 counts	16 counts	5 counts
6,984	6,468	6,260	5,877	6,621	7,000

These figures are not so low as those given by some authors (Hayem and Khetagurow), but they show clearly the absence of leucocytosis and the tendency toward a slight progressive diminution in the number of leucocytes during the progress of the disease. They do not show the leucocytosis in the early stages and at the beginning of convalescence, which some have assumed to exist.

One should not, however, overestimate the value of such a table as this for fixing a true mean. It should be remembered that slight and unimportant circumstances—baths, for instance—may cause a temporary increase in the number of leucocytes per cmm. to many times the normal number, where a fall of this extent is, of course, impossible. The effect of this in any large number of counts would be, of course, to give a mean which is really a trifle above the usual normal number. In *stained specimens* the red corpuscles show either a normal condition or those changes common to any secondary anæmia. The colorless corpuscles, however, show markedly the interesting changes in the relative proportion of the different varieties which have been pointed out by Ouskow and referred to above, namely, a progressive diminution in the percentage of multinuclear ("over-ripe") elements, with a relative increase in the large mononuclear leucocytes ("ripe elements"). This condition may not be well marked in the first or second weeks, but becomes more so as the fever continues. At its height it forms a striking picture on the examination of the blood. The only difference between our results and those of Ouskow and Khetagurow is that we have been rather inclined to estimate the proportion of large mononuclear leucocytes and transitional forms ("ripe elements") as compared to the small mononuclear forms (lymphocytes, small transparent forms)—("young elements")—a little

higher than these two observers. Among the few cases where careful differential counts of over 1000 leucocytes were made, the average number of over-ripe elements was as follows:

Second week.	Third week.	Fourth week.	Fifth week.	Sixth week.
5 counts	1 count	3 counts	1 count	2 counts
71.7 per cent.	66.5 per cent.	65.3 per cent.	58.6 per cent.	53.4 per cent.

These results were wholly confirmed by a considerable number of superficial counts of one or two hundred leucocytes. In all of these cases the proportion of the large mononuclear elements was markedly increased.

From a diagnostic point of view the condition of the red corpuscles and the hæmoglobin in the blood of typhoid fever is of little importance. On the other hand, the examination of the leucocytes numerically and histologically may give us valuable help. The commonest conditions with which typhoid fever may be confounded are perhaps (1) malarial fever, (2) tuberculosis in various forms, (3) typhus fever, (4) other infectious processes of various kinds—general or local—when the seat of infection is not evident.

The examination of a fresh specimen of blood will enable us to distinguish the case from *malarial fever* by the absence of the hæmatozoa. In *tuberculosis* when there is any local inflammatory process such as exists in the great majority of cases, there is always a certain degree of leucocytosis, showing a distinct increase in the number of over-ripe elements. In the cases of general acute miliary tuberculosis this is also probably the rule. In some rare cases of acute miliary tuberculosis, where the primary focus of infection is not the seat of an inflammatory process of any extent, the leucocytosis may be absent, but in two cases of this sort reported by Ouskow[12], though it is not stated whether there was a leucocytosis or not, there were respectively 82 and 83 per cent. of multinuclear leucocytes. *Typhus* fever, according to Ouskow (*l. c.*) (three cases), shows no appreciable change in the blood from the normal. The majority of the other *infectious processes* with which typhoid fever may be confounded are usually associated with hidden inflammatory foci. In such cases there is almost always a marked leucocytosis with an increased proportion of multinuclear neutrophiles. In some cases of malignant pneumococcus infection* there is an absence

* This may possibly be true in some other malignant general infections (streptococcus).

of the leucocytosis, though, so far as I know, a subnormal number of leucocytes has never been noted, nor a diminution in the proportion of "multinuclear" neutrophiles.

The examination of the blood should never be neglected in any suspected case of typhoid fever. In the absence of leucocytosis and the change in the relative proportion of the different varieties of colorless corpuscles, one to another, we have two valuable points which, while neither may be pathognomonic, are of considerable diagnostic value. The change in the relative proportion of the leucocytes is particularly striking where the case has existed for some time and has perhaps shown anomalous symptoms. Here the discovery of a much reduced percentage of "multinuclear" elements with a corresponding increase in the large mononuclear and transitional forms, may be the deciding point in the diagnosis.

Literature.

1. Andral: Clinique médicale. 8vo. Paris, 1834, 3me édition, vol. I, p. 95.
2. Le Canu: Études chimiques sur le sang humain. 4to. Thèse de Paris, 1837.
3. Raciborski: Gaz. méd. de Paris, 1839, p. 82.
4. { Andral and Gavarret: Annales de chimie et de physique, vol. LXXV, p. 184, 1840.
   { Andral: Essai d'hématologie pathologique. 8vo. Paris, 1843.
5. Simon: Physiolog. u. patholog. Anthropochemie. 8vo. Berlin, 1842.
6. Thompson: In Cormack: The natural history of the epidemic fever, etc. 8vo. London, 1843.
7. Bequerel and Rodier: Recherches sur la composition du sang dans l'état de santé et dans l'état de maladie. 8vo. Paris, 1844 and 1846.
8. Popp: Untersuchungen über die Beschaffenheit des menschlichen Blutes in verschiedenen Krankheiten. 8vo. Leipzig, 1845.
9. Virchow: Med. Zeitung, Berlin, 1847, Nos. 3 and 4, and Gesammelte Abhandlungen. 8vo. Frankfurt, 1856.
10. Jansen: Nederl. Lancet, Gravenh., 1847–8, 2 S., iii, 522–530.
11. Otto: Beitrag zu den Analysen des gesund. Blut. Inaug. Diss. 8vo. Wurtzburg, 1848.
12. Durozier: Gaz. des Hôp. Paris, 1853, pp. 601 and 605.

13. Welker: Ueber Blutkörperchenzählung. (Archiv d. Vereins f. gemeinschaftl. Arbeiten, Bd. I, p. 161, 1853.) Jahresber. 1853, I, 29.
14. Welker: Pragerviertcljahrschrift, 1854, Bd. IV, p. 57.
15. Denis (de Commercy): Mémoire sur le sang, etc. 8vo. Paris, 1859, pp. 146–51.
16. Jaccoud: De l'humorisme ancien comparé a l'humorisme moderne. Thèse d'aggrégation. 4to. Paris, 1863.
17. Ernesti: Anaemiae post typhum abdominalem exortae exemplum. Inaug. diss. 8vo. Gryphiswaldiae, 1864.
18. Sée: Du sang et des anémies. 8vo. Paris, 1866.
19. Virchow: Cellularpathologie. 8vo. Berlin, 1871.
20. Naunyn: Corresp. Bl. f. Schweitzer Aerzt., 1872, No. 14, p. 300.
21. Quincke: Virchow's Archiv, Bd. 54, pp. 537–545, 1872.
22. Quinquaud: Compt. rend. d. l'Acad. d. Sciences, Paris, 1873.
23. Gautier: Chimie appliquée à la physiologie. 8vo. Paris, 1874.
24. Eichorst: Deutsch. Archiv f. klin. Med., Vol. 14, p. 223, 1874.
25. Bonne: Variation du nombre des globules blancs, etc. 4to. Thèse de Paris, 1875.
26. Brouardel: Bull. et Mém. Soc. méd. d. hôp. de Paris, 1876, 2 s., XIII, 177–184.
27. Sörensen: Untersögelser om Antallet af röde og hvide Blodlegemer under forskjellige physiologiske og pathologiske Tilstande. Kjöbenhavn, 1876. Quoted by Reinert: Die Zählung der Blutkörperchen, etc. 8vo. Leipzig, 1891.
28. Ehrlich: Farbenanalytische Untersuchungen z. Histologie u. Klinik des Blutes. 8vo. Berlin, 1891. For special references to his earlier and later works and to those of his pupils *vide* Müller: Centralblatt für allgem. Path. u. path. Anat., 1892, 19 and 20, and Thayer: Remarks on the clinical value of Ehrlich's methods, etc., Bost. Med. and Surg. Journ., 1893, Feb. 16th and 23rd.
29. Leichtenstern: Untersuchungen über den Hæmoglobingehalt des Blutes in gesunden und kranken Zuständen. 8vo. Leipzig, 1878.
30. Arnheim: Jahrbuch der Kinderheilkunde, N. F., XIII, 1879, p. 293.
31. Baxter and Willcocks: Lancet, 1880, Vol. 1.
32. Zaeslein: Blutkörperchenzählung u. Blutfarbstoff best. bei Typhus abdominalis. Inaug. Diss. Basel, 1881. 8vo.

33. Halla: Zeitschr. f. Heilk., Prag, Bd. IV, 1883, p. 198.
34. Laache: Die Anaemie. 8vo. Christiania, 1883.
35. Robin, quoted by Hutinel: Étude sur la convalescence et les rechutes de la fièvre typhoide. 8vo. Paris, 1883. (Thèse d'aggrégation.)
36. Malassez: Unpublished notes quoted by Hutinel: Étude sur la convalescence et les rechutes de la fièvre typhoide. 8vo. Paris, 1883.
37. Holst: St. Petersburger med. Woch., 1885, N. F., II, 1–4.
38. Leclerc: À propos des traitements de la fièvre typhoide, etc. Lyon Méd., 1887, LVI, 494–501.
39. Ollivier: Semaine Méd., 1887, p. 504.
40. Tumas: Deutsch. Archiv f. klin. Med., 1887, Bd. 4, p. 323.
41. Hayem: Le sang. 8vo. Paris, 1889.
42. Pée: Ueber Leucocytose. Inaug. Diss. 8vo. Berlin, 1890.
43. Ouskow: The blood as a tissue (Russian). 8vo. St. Petersburg, 1890.
44. Lafleur: On pyrodin. The Johns Hopkins Hospital Reports, Vol. II, 1890.
45. Gabritchewsky: Archiv f. experiment. Pathol. u. Pharmak., Bd. 28, H. 1, 2, p. 183, 1890.
46. Khetagurow: Pathological changes in the blood in typhoid fever. Inaug. diss. St. Petersburg, 1891. Summary in Virchow's Archiv, Bd. 120, F. XII, B. VII, 187.
47. Reinert: Die Zählung der Blutkörperchen, etc. Leipzig, 1891.
48. Hölscher: Münchener med. Woch., 1891, XXXVIII, 43, 62.
49. Thayer: Boston Med. and Surg. Journ., Feb. 16th and 23rd, 1893.
50. Winternitz: Centralblatt f. klin. Med., March 4th, 1893.
51. Thayer: The Johns Hopkins Hosp. Bull., No. 30, 1893.
52. Emelianow: Archives des sciences biologiques, St. Petersburg, 1893.
53. Thayer: The Johns Hopkins Hosp. Bull., No. 31, 1893.